"the references disclose the racemate of the claimed levorotatory compound, therapeutic compositions thereof and useful in treatment awakening disorders and of confusion especially in the elderly. The claimed optical isomer would be obvious from the racemate containing it in the absence of any unobvious properties. It would be quite obvious to use the particular optical isomer which had the greater activity.

In response to the arguments of Applicant, the Examiner contends:

"While the levorotatory isomer may exhibit better bioavailability than the racemate or dextroratatory isomer, it is not unexpectedly or surprisingly better. There is no showing especially with respect to the compositions claims directed to central nervous stimulants. Moreover, Lafon II would suggest the use of the compounds for treating Alzheimers disease since the reference disclose that the compounds thereof are useful in treating confusion especially in older people."

Issue must be taken with the position of the Examiner since the very significant differences between the claimed levorotatory isomer and the racemate or dextrorotatory isomer appear to have been misconstrued and the surprising and unexpected pharmacological properties are simply disregarded, as will be shown below.

Firstly, it is known that the activity of the racemic (Ar) is half of the sum of the activities of

the levorotatory (A_l) and detrorotatory (A_d) compounds, namely $A_r = (A_l + A_d)/2$.

In the instant invention, the facts show that the pharmacokinetic values AUC_o^{+9h} (area under the curve from time T = O to time T = +9h) of metabolite compounds (CRL 40 476 and CRL 40 467) determined after administration of the racemic compound (CRL 40 476 - "CP 2"), the levorotatory compound (CRL 40 982 - "EX 1") and respectively the dextrorotatory compound (CRL 40 983 - "CP 2") are such that unexpectedly the AUC_o^{+9h} of the racemic product (CP 2) does not correspond to half the sum of AUC_o^{+9h} for "EX 1" and AUC_o^{+9h} for "CP 1".

To be more specific, as shown by the Table I data (Page 12); when considering CRL 40 476 as the metabolite compound the value of:

$$(AUC_o^{+9h} \text{ "EX 1"} + AUC_o^{+9h} \text{ "CP 1"})/2 =$$

$$(97.22 + 50.96)/2 = 74.08$$

which is clearly different from the value AUC_o^{+9h} for "CP 2" of 46.76 determined for the racemic compound (see Table 1).

Further, when considering CRL 40 467 as the metabolite compound, which is inactive (see page 9, lines 2 to 9), the value of:

$(AUC_o^{+9h}$ "EX 1" + AUC_o^{+9h} "CP 1")/2 = (8.69 + 83.12)/2

= 44.91

again is significantly different from the value of AUC_o^{+9h} of 55.12 determined for the racemic compound (CP 2) in the preparation of the inactive metabolite.

These results confirm that the levorotatory compound "Ex 1" exhibits surprisingly better bioavailability than the bioavailability of the racemic compound "CP 2" and the dextrorotatory compound "CP 3", which is certainly unexpected.

Applicant's specification in detail describes and demonstrates by comparative assays the unexpected properties of the claimed levorotatory compound. In this connection, attention of the Examiner is respectfully directed to the disclosure appearing at pages 8, line 26 to page 11, line entitled D - PHARMACOKINETIC STUDY, and the data reported in TABLE I appearing on page 12. Moreover, contrary to the contention of the Examiner, the results of Clinical Trials described, for example, at page 11, lines 3 to 6 namely:

> "In human clinical trials, it was found that the elimination half-life of CRL 40 982 is relatively long (about 10 h), making it possible to obtain good results on adults with 1 to 2 administrations per day."

show some of the unexpected advantages of the claimed compositions directed to central nervous system stimulant.

It is respectfully submitted that Applicant has demonstrated and described in detail the surprising and unexpected properties of the claimed levo isomer compound in comparison with the properties determined for the racemic compound or the dextro isomer. In this connection the properties actually observed have been shown to significantly differ from those calculated by known techniques. Moreover, contrary to the urging of the Examiner, separation of the racemate into its isomers by isolation is not technically possible (see page 2, lines 32 to 33) and the levo isomer must be specifically prepared by chemical synthesis. Thus, merely isolating the racemate into its isomer components is not technically possible and known techniques for calculating activity of the levo isomer, the dextro isomer and the racemate compound have been shown to inaccurately predict those actually observed; the unexpected properties of the levo isomers compound would

be apparent. No incentive is provided for separately synthesizing the isomer components and while it may be suggested, or even obvious to try, to prepare the isomers, "obvious to try" is not obviousness under 35 U.S.C. 103.

For the foregoing reasons, reconsideration of the rejection of claims 1 and 8 - 10 under 35 U.S.C. 103 is respectfully requested.

Claims 3 and 4 have been rejected under 35 U.S.C. 103 as being unpatentable over Lafon I and II for the reasons given in rejecting claims 1 and 8 to 10 over these references. This rejection is respectfully traversed.

The Examiner maintains that:

> "Since the compounds of the reference, i.e. the racemic mixture are useful in treating awakening disorders and confusion in the elderly, it would be obvious that the particular isomer which contributed most to these actions would be employed. It would be obvious to separate the racemate into isomers and determine which was the most active. No unobvious or unexpected properties have been shown."

As discussed in detail with regard to the rejection of claims 1 and 8 to 10, the levo isomer compound has been shown to exhibit properties which would not be predicted by known techniques for calculating activity of the racemate (AUC_{0}^{+9h}) and neither isomer could

be prepared by mere isolation from the racemate. Thus, it has been demonstrated that the claimed levo isomer compounded does indeed exhibit unexpected properties and such unexpected properties could only be determined by actual observation after chemical synthesis of the individual isomer compound.

Moreover, the Examiner's position that since the compounds of the references are disclosed as being useful in treating awakening disorders and confusion in the elderly would make obvious applicant's claimed invention is not well taken. The references do not provide other than a broad general suggestion of possible use in treating certain diseases in the elderly. Neither reference, however, discloses the use of the racemate compound in the treatment of Alzheimer's disease and certainly does not disclose or suggest the use of the claimed levo isomer compound for such purpose. In applicant's specification at page 11, lines 20 to 22 are discussed the symptoms of Alzheimer's disease which are different from merely confusion in the elderly. Again it is urged that "obvious to try" is not obviousness under 35 U.S.C. 103.

It is respectfully submitted that for the foregoing reasons, the rejections of claims 3 and 4 under 35 U.S.C.